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Nutrition and lung cancer

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Epidemiologic evidence on the relationship between nutrition and lung cancer is reviewed. Observational studies of diet and lung cancer, both prospective and retrospective, continue to suggest strongly that increased vegetable and fruit intake is associated with reduced risk in men and women; in various countries; in smokers, ex-smokers, and never-smokers; and for all histologic types of lung cancer. Prospective studies of blood β-carotene levels, arguably the best available biomarker of vegetable and fruit intake, indicate that low levels are predictive of increased lung cancer incidence. However, in a randomized, placebo-controlled clinical trial in male smokers, lung cancer incidence and total mortality were increased significantly among the men receiving β-carotene supplements. If β-carotene can prevent lung carcinogenesis, which the trial cannot rule out, then the dosage, duration of use, method of administration, and/or subpopulation are critical. Ongoing clinical trials, some of which include women, will provide much-needed information. Other carotenoids, other phytochemicals, and associated dietary patterns may explain the beneficial effects of vegetables and fruits and have not been explored adequately in epidemiologic work. Several observational epidemiologic studies, both prospective and retrospective, have indicated that diets high in fat, saturated fat, and cholesterol may increase the risk of lung cancer and that the effect is not mediated through vegetable and fruit intake. The relationship, although not yet established, merits further investigation. Since β-carotene can function as an antioxidant, other micronutrients with this potential, specifically vitamins E and C and selenium, also have been proposed to reduce lung cancer risk. However, the totality of the epidemiologic evidence is not, at present, persuasive for any one of these micronutrients. *Cancer Causes and Control* 1996, 7, 157-177

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Introduction

Lung cancer has been the leading cause of cancer death in United States men since the early 1950s, and became the leading cause of cancer death in US women in 1987.[1] The American Cancer Society estimates that 169,900 Americans will be diagnosed with lung cancer in 1995.[1] Lung cancer is also the most common tumor worldwide.[2] Prevention, early detection, and treatment are three approaches for reducing cancer-related morbidity and mortality. Early detection of lung cancer has not been successful as symptoms often do not appear until the disease is advanced; only 15 percent of lung cancers are discovered while the disease is still localized.[1] Treatment also is not effective; the five-year relative survival rate for lung cancer is only 13 percent.[1] These statistics emphasize that the only viable strategy, at present, for reducing lung cancer mortality is prevention.

Cigarette smoking has been established as the dominant risk factor for lung cancer; 90 percent of lung cancer deaths in US men and 79 percent in US women are attributable to cigarette smoking.[3] Encouraging nonsmokers not to start and current smokers to quit is of primary importance in reducing lung cancer incidence and mortality. Other risk factors for lung cancer include environmental tobacco smoke; previous lung disease; occupational exposures including arsenic, asbestos, chloromethyl ethers, and nickel; radon; air pollution; and genetic susceptibility.[4] In addition, evidence from descriptive studies, prospective, and retrospective studies

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strongly suggests that dietary factors are important in the etiology of lung cancer.

Vitamin A and β-carotene: a historical perspective

Experiments with animal models conducted in the 1960s and 1970s demonstrated that high doses of retinoids (synthetic vitamin A analogs) could inhibit carcinogenesis in several organs, including the respiratory tract.[5] Thus, early studies of diet and lung cancer in human populations evaluated the importance of vitamin A, but at the lower levels of intake that characterize typical diets. Bjelke,[6] in a cohort of Norwegian men, and Mettlin *et al*,[7] in a case-control study among White male hospital patients in New York (USA), demonstrated that computed indices of total vitamin A intake were associated significantly with reduced lung cancer risk after adjusting for smoking. In both studies, milk and carrots contributed substantially to vitamin A intake; and each were related strongly and inversely to risk.[6-8] Thus, not only the retinol (preformed vitamin A) in milk but also the provitamin A carotenoids (carotenoids that can be metabolized to vitamin A) in carrots were thought to be protective. Two other early epidemiologic studies, a hospital-based case-control study in Singapore Chinese[9] and a cohort study in Japan,[10] both conducted in men and women, found that increased consumption of vegetables, specifically green leafy vegetables[9] or green or yellow vegetables rich in carotenoids,[10] was associated significantly with reduced lung cancer risk.

Subsequently, in 1981, Peto and coauthors,[11] noting the protective effects of increased vegetable consumption in epidemiologic studies of lung and other cancers, speculated that β-carotene, the most abundant and efficiently converted of the provitamin A carotenoids in vegetables and fruits, might protect against cancer. The hypothesis was attractive since blood β-carotene levels, in contrast to blood retinol levels, could be modulated with diet and the chemopreventive potential of supplemental β-carotene could be evaluated in randomized clinical trials. It was emphasized that if β-carotene were to function as an antioxidant or free radical scavenger in humans, as it does in plants, conversion into retinol would not be a prerequisite for biologic activity.

The first cohort[12] and case-control[13,14] studies to evaluate the independent contributions of provitamin A carotenoids and retinol in the diet revealed that reduced lung cancer risk was associated only with increased intake of the carotenoids. In both studies, the inverse trends were statistically significant, even after adjusting for smoking duration; were most evident in cigarette smokers; and were within the ranges of carotenoid intake characteristic of typical, unsupplemented US diets.[12,14] In the cohort study conducted among male electric company workers in Chicago (IL, USA), Shekelle *et al*[12] demonstrated that other nutrients were not related significantly to lung cancer incidence. In the population-based case-control study in New Jersey (USA) White men, Ziegler and collaborators[14] pointed out that the inverse trend with frequency of consumption of vegetables and fruits was as strong as that with provitamin A carotenoid intake. The importance of the plant sources of vitamin A was corroborated in a population-based case-control study of lung cancer conducted in Hawaii (USA)[15,16] where increased intake of provitamin A carotenoids was as protective as increased intake of all sources of vitamin A.

Biochemical techniques, as well as dietary assessment, were utilized to test the β-carotene hypothesis; several cohort studies had stored blood in which carotenoids could be directly measured. In the first analyses, involving a multicenter US hypertension cohort,[17] total serum carotenoids, measured spectrophotometrically, were found not to be related to subsequent lung cancer incidence (17 cases). However, in the next three analyses, involving Swiss men (35 lung cancer cases),[18] Japanese-Hawaiian men (74 cases),[19] and men and women living in a Maryland (USA) county (99 cases),[20] prediagnostic serum or plasma β-carotene levels, measured by high-performance liquid chromatography (HPLC), were significantly lowered in the participants who developed[19,20] or died[18] from lung cancer. In the Nomura[19] and Menkes[20] studies, the inverse trends with serum β-carotene remained significant after adjusting for smoking; and examination of the relationship over time suggested that preclinical disease was not responsible for the effect. In all four cohorts, blood retinol levels were not associated with subsequent lung cancer incidence.

A number of reviews,[21-27] published around 1990, have summarized the research on diet and lung cancer during this period. The consensus was that observational studies of diet and lung cancer, whether prospective or retrospective, consistently demonstrated reduced risk with increased intake of carotenoids, vegetables, and fruits. Further, high levels of β-carotene in the blood were consistently associated with reduced incidence of lung cancer in prospective studies. The simplest explanation of the epidemiology was that β-carotene was protective although other carotenoids, other constituents of vegetables and fruits, and associated dietary patterns had not been adequately explored.[27,28] On the basis of the consistency of the epidemiologic findings, the evidence for tumor inhibition in animal models, and some plausible mechanisms, clinical trials[29] were initiated in the 1980s to evaluate the potential of β-carotene in the prevention of lung and other cancers. At the time, the linkage between β-carotene and lung cancer was believed widely

to be the most persuasive finding from epidemiologic studies of diet and cancer.

Vegetables, fruits, and carotenoids

Recent evidence

Ever-increasing numbers of prospective (Table 1) and retrospective (Table 2) dietary studies have evaluated the role of vegetables and fruits, carotenoids, and related micronutrients in the etiology of lung cancer. In all eight prospective studies[8,12,30,32,34-37] and 18[14,15,38,40-50,52,53,55,57] of 20[51,56] retrospective studies, lung cancer risk was reduced at high levels of vegetable and/or fruit consumption, or at high intake of carotenoids or vitamin C, which are markers of vegetable and fruit intake. However, on closer examination, the protective effect was restricted to a subset of the study population in several studies, (*e.g.*, only men,[15] women,[32] or Whites,[39,40]) or was too weak to be persuasive in the absence of corroborating studies.[36,43] Other epidemiologic studies,[9,10,58-62] generally with more limited dietary assessment techniques than the studies identified in the Tables, have shown reduced lung cancer risk in individuals with increased intake of specific vegetables and/or fruits; but measures of nutrient or food group intake were not provided.

No new analyses of blood β-carotene levels and subsequent lung cancer incidence have been published recently (Table 3). Instead, several groups have acknowledged extensive degradation of β-carotene in serum or plasma stored at $-20°C$.[69,75,77] Only one[74] of six studies of prediagnostic blood β-carotene levels has failed to find a striking inverse relationship with lung cancer; and it stored samples at $-20°C$, rather than $-70°C$. Several epidemiologic studies have measured blood micronutrient levels in lung cancer patients, but are difficult to interpret because of the possible systemic consequences of this disease and its treatment.

In recent years, more studies of diet and lung cancer have evaluated both provitamin A carotenoid intake and vegetable and fruit intake. In New Jersey men, the smoking-adjusted relative risks (RRs) for smokers in the lowest, relative to the highest, quartile of intake, were 2.2, 1.8, 1.8, and 1.7 for yellow-orange vegetables, dark green vegetables, vegetables and fruits, and estimated provitamin A carotenoids, respectively.[14] In a multi-ethnic Hawaiian population, stronger inverse trends in lung cancer risk were seen for total vegetable intake than for provitamin A carotenoids, for any other micronutrient, for any vegetable subgroup, or for any single vegetable.[47] In a study[37] of postmenopausal Iowa women, lung cancer risk was doubled in women with low intake of all vegetables and fruit, all vegetables, or green leafy vegetables; comparable protective effects were not observed for provitamin A carotenoid or vitamin C intake or for foods rich in β-carotene, lutein, or lycopene. Thirteen[30,32,35-37,39,43,45,47,49,50,53,57] of 15[12,52] prospective and retrospective studies of diet and lung cancer have found notably stronger inverse trends with vegetable and fruit intake than with estimated provitamin A carotenoid intake. Even though imprecision in portion sizes and nutrient composition databases complicates the calculation of nutrient intake, summed frequencies of consumption of specific foods are likely to be even less accurate in predicting intake of a specific nutrient. Thus, provitamin A carotenoids do not explain completely the association of vegetable and fruit consumption with reduced lung cancer risk consistently observed in epidemiologic studies. Other phytochemicals (compounds in vegetables and fruits) and a variety of protective factors seem to be involved.

Food composition data for the five major carotenoids in foods were recently compiled; only analytic results meeting specified criteria were included.[79,80] Prior to publication of this database, analyses of diet and lung cancer relied on the US Department of Agriculture (USDA) measurements of provitamin A carotenoids in foods, which generally detected β-carotene, α-carotene, and several other chemically similar carotenoids. Two population-based case-control studies of lung cancer, which previously had demonstrated reduced risk with high levels of provitamin A carotenoid intake,[14,47] have utilized the new database to evaluate whether β-carotene is uniquely protective.[81,82] In a multi-ethnic Hawaiian population, Marchand *et al*[81] observed significant inverse trends in risk for intake of β-carotene, α-carotene, and lutein, in both men and women. In New Jersey White men, Ziegler and collaborators[82] found significant inverse trends for the two carotenes, and a marginally significant effect for lutein. Intake of these carotenoids was correlated highly in both populations; however, both analyses suggested that the individual carotenoids had distinct, independent effects. Further, in both studies, high intake of a variety of vegetables – measured either as concurrently high intake of two vegetable subgroups[82] or as elevated total vegetable intake[81] was associated with reduced lung cancer risk more strongly than high intake of the important individual carotenoids. Although HPLC techniques have been developed to separate and quantitatively measure the major individual carotenoids in human serum and plasma,[83] and are being utilized in prospective studies, results have not yet been published.

Early prospective[8] and retrospective[14,47] studies of diet and lung cancer suggested that vegetables, especially the dark green and yellow-orange vegetables rich in β-carotene, reduced lung cancer risk; however, more recent investigations have shown similar patterns in risk reduction with fruit intake.[30,32,34,37,39,45,46,50,53,57] The rela-

Table 1. Prospective studies of vegetable, fruit, carotenoid, and micronutrient intake and lung cancer[a,b,c]

Study (ref)	Year	Location Population	No. of cases	Years of follow-up[d]	Dietary assessment[e]	Vegetables + fruits	Vegetables	Fruits
Bjelke, *et al* [6]	1975	Norway	M + F: 153	9-12	FFQ		↓	0
Kvale, *et al* [8]	1983							
Shekelle, *et al* [12]	1981	Chicago, IL	M: 33	19	DH		↓?	↓?
Kromhout, *et al* [30]	1987	Netherlands	M: 63	25	DH			↓↓↓
Paganini-Hill, *et al* [31]	1987	Los Angeles, CA, USA	M: 125	8	FFQ	↑	↑	↓
Shibata, *et al* [32]	1992	Retirement community	F: 70			↓	↓↓	↓↓
Shibata, *et al* [33]	1992							
Fraser, *et al* [34]	1991	California, USA Seventh-day Adventists	M: 61	6	FFQ			↓↓↓
Knekt, *et al* [35]	1991	Finland	M: 117	14-20	DH		↓?	↓?
Chow, *et al* [36]	1992	USA White Lutherans	M: 219	20	FFQ		↑	↓
Steinmetz, *et al* [37]	1993	Iowa, USA 55+ years old	F: 138	4	FFQ	↓↓↓	↓↓↓	↓↓

Continued (opposite)...

tive contribution of more narrow vegetable and fruit subgroups to lung cancer prevention has not been systematically investigated. Steinmetz and Potter[84] identified a number of phytochemicals, such as flavonoids, phenols, indoles, dithiolthiones, and isothiocyanates, which, on the basis of animal and *in vitro* experiments, might be important in human cancer prevention. However, evaluating these dietary factors in epidemiologic studies is complicated by the imprecision of dietary assessment, the limited data on levels of non-nutrient phytochemicals in specific foods, and the lack of biomarkers. One of the few vegetable and fruit subgroups relatively easy to assess is the *Allium* family, which is rich in organic sulfides. Recently, the Netherlands Cohort Study investigators reported[85] that in 484 lung cancer cases diagnosed during 3.3 years of follow-up, onions and leeks and garlic supplements were not consistently associated with reduced incidence after adjusting for smoking.

Generalizability of effect

Whether the reduced risk that is associated with increased vegetable, fruit, and carotenoid intake (whatever the cause) is observed for all lung cancers has etiologic and public health implications. Substantial inverse associations have been observed in ex-smokers,[34,37,40,42,57] as well as current smokers.[14,37,39,42,47] Nonetheless, such results do not imply necessarily that dietary modification after quitting smoking is effective in reducing risk since the ex-smokers with elevated vegetable, fruit, and carotenoid intake probably also had high intakes while actively smoking. Never-smokers are too few in number in most lung cancer studies for reliable risk estimates. However, in five[34,46,50,53,57] of six[56] studies focused on never-smokers, conducted in women from Hong Kong,[46] Greece,[50] and Florida (USA),[53] and in men and women from California Seventh-day Adventists[34] and New York State,[57] increased intake of vegetables, fruits, and carotenoids has been associated with reduced lung cancer risk, with effects similar in magnitude to those generally observed among active smokers.

Diet has been investigated in only one occupationally exposed population. In male residents of a Chinese mining community, among whom radon and arsenic exposures act synergistically with heavy cigarette and pipe use, dark-green vegetable intake was associated significantly and inversely with lung cancer risk.[55] It is intriguing that, of the few lung cancer studies that have failed to observe a lowered risk agssociated with diets high in vegetables and fruits, two[43,51] were conducted in Chinese women among whom cigarette smoking accounted for only 24 to 35 percent of all lung cancer and two uncommon exposures – chronic lung disease (*e.g.*, tuberculosis, pneumonia, or emphysema) and cooking oil fumes – contributed substantially to their risk.

Early observational studies of lung cancer suggested that increased intake of carotenoids, vegetables, and fruits reduced risk only in men and only in Whites. Strong inverse relationships characterized studies of lung cancer in men in Chicago,[12] New Jersey,[14] and the Netherlands,[30] while early studies of lung cancer in females in Los Angeles[41] and China[43] produced ambiguous results. In addition, in case-control studies conducted among both genders in Hawaii[15] and New York State,[42] inverse associations were observed in men, but not in women. However, in more recent studies, among women living in Hong Kong,[46] Hawaii,[47] Greece,[50] Florida,[53] and Iowa,[37] trends in risk with intake of carotenoids, vegetables, or fruit clearly were inverse and generally significant. Moreover, stronger inverse associations in women than in men have now been reported in studies conducted in Los Angeles,[32] New Jersey,[39] and New York State.[57]

Table 1. Continued

Dark green vegetables	Yellow-orange vegetables	Carotenoids	Retinol	Vitamin A	Vitamin C	Total vitamin C	Vitamin E	Total vitamin E
	↓↓			↓↓↓	0			
		↓↓↓	0		↓?			
		0	0		↓↓↓			
↑	↓	0			0	0		0
↓↓	↓↓	↓↓			↓↓	↓↓		↓↓
0	↓?	↓?	↑?	↑?	0		0	
	↓	0	0	0	↓			
↓↓↓	↓	↓			0	0		

[a] To be included, studies had to assess diet in sufficient detail for the intake of several food groups and/or micronutrients to be evaluated. When sequential analyses of one cohort have been published, results based on the largest number of lung cancer cases or deaths are used.

[b] ↓↓↓ (and ↑↑↑) indicate inverse (and positive) associations with statistically significant trends. ↓↓ (and ↑↑) indicate inverse (and positive) associations with marginally significant trends or apparent trends that do not reach statistical significance. ↓ (and ↑) indicate inverse (and positive) associations with no evidence of a trend. ↓? (and ↑?) indicate inverse (and positive) associations with insufficient data presented to evaluate trend. 0 indicates no association.

[c] None of these studies assessed folate or fiber intake. Carotenoids, retinol, vitamin A, vitamin C, and vitamin E refer to intake from foods. Total vitamin C and total vitamin E refer to combined intake from foods and supplements.

[d] M: males; F: females.

[e] FFQ: food frequency questionnaire; DH: diet history.

Inverse associations of vegetable, fruit, and carotenoid intake with lung cancer risk are seen more consistently in both genders than across racial subgroups. A population-based case-control study conducted in New Jersey found reduced lung cancer risk in Whites but not in Blacks,[39] although a hospital-based case-control study in Louisiana (USA)[45] reported reduced risk in both races. In a third study in New Mexico (USA) Whites and Hispanics,[40] the inverse association was restricted to Whites. Studies in Asians have been somewhat consistent, with inverse associations noted in five[9,10,19,46,55] of seven studies.[43,51] In the New Jersey study, neither smoking patterns nor lung cancer histology explained the discrepancy between Blacks and Whites.[39,41] Genetic variation in carcinogen metabolism leading to differential lung cancer susceptibility[86] was proposed as a possible explanation, although the problems of using dietary assessment designed for Whites in Black populations, and other methodologic difficulties, also were emphasized.[39]

Although vitamin A is essential for the normal differentiation of squamous epithelium,[5] and early studies of lung cancer, using total vitamin A indices, reported especially strong inverse associations with squamous cell tumors,[8,38] one consistent finding of observational studies of lung cancer is that the reduced risk associated with diets high in vegetables, fruits, and carotenoids is not restricted to squamous cell tumors. Of the studies that have investigated histologic specificity, nearly all have found inverse associations not only with squamous cell lung cancer but also with lung adenocarcinomas[19,34,37,39,41,42,47,49-51,55,57] and/or small cell lung cancer.[19,37,39,45,47] Only a minority[20,42,47,57] of the studies have demonstrated substantially stronger inverse associations with squamous cell disease than with other lung cancer histologies.

In summary, diets high in vegetables, fruits, and carotenoids have been associated with reduced lung cancer risk in men and women; in various countries; in Whites and Asians (though not necessarily in Blacks or Hispanics); in current, ex-, and never-smokers; and for all histologic types. The consistency of the relationship is remarkable. Although many investigators have postulated differential effects by gender, race, smoking history, or histologic subtype – and subtle differences cannot, at present,be ruled out – many discrepancies may be attributable to small numbers in specific subgroups, analytic decisions, and chance. In addition, our understanding of the etiology should not be overestimated. When the cause(s) are unknown, assessment is imperfect and will measure the critical exposures with variable accuracy in different subpopulations. In fact, fluctuations in the strength of the dietary associations among racial/ethnic subgroups may be providing important clues about the underlying etiology.

Table 2. Retrospective studies of vegetable, fruit, carotenoid, and micronutrient intake and lung cancer[abc]

Study (ref)	Year	Location Population	No. of cases[d]	Study design[e]	Dietary assessment[f]	Vegetables + fruits	Vegetables	Fruits	Dark green vegetables	Yellow-orange vegetables	Carotenoids	Retinol
Mettlin, *et al*[7]	1979	Buffalo, NY, USA	M: 427	Hos	FFQ						↓?	↓?
Byers, *et al*[38]	1984											
Hinds, *et al*[15]	1984	Hawaii, USA	M: 261	Pop	DH						↓?	
Kolonel, *et al*[16]	1985	Multi-ethnic	F: 103								↑?	
Ziegler, *et al*[13]	1984	New Jersey, USA	WM: 736	Pop	FFQ	↓↓↓	↓↓↓	↓	↓↓↓	↓↓↓	↓↓	↑
Ziegler, *et al*[14]	1986	Whites & Blacks	WF: 860				↓↓↓	↓↓↓			↓↓↓	
Dorgan, *et al*[39]	1993		BM: 269				0	↑↑↑			↑	
			BF: 86				↓	↑			↑↑	
Samet, *et al*[40]	1985	New Mexico, USA	WM+F: 322	Pop	FFQ						↓↓	0
		Whites & Hispanics	HM+F: 125								↑	0
Wu, *et al*[41]	1985	Los Angeles, CA, USA Whites	W: 210	Com	FFQ						↓?	0
Byers, *et al*[42]	1987	Western New York, USA	M: 296	Pop	FFQ						↓↓↓	
			F: 154								0	
Gao, *et al*[43]	1987	Shanghai, China	F: 672	Pop	FFQ				↓?		↑	
Pastorino, *et al*[44]	1987	Milan, Italy	F: 47	Hos	FFQ						↓?	↓?
Fontham, *et al*[45]	1988	Louisiana, USA Whites & Blacks	M+F: 1253	Hos	FFQ	↓↓↓	↓↓	↓↓↓			0	0
Koo, *et al*[46]	1988	Hong Kong Chinese Never-smokers	F: 88	Com	FFQ			↓↓↓	↓	↓		
Le Marchand, *et al*[47]	1989	Hawaii, USA	M: 230	Pop	DH		↓↓↓	0	↓↓↓	↓↓↓	↓↓↓	0
		Multi-ethnic	F: 102				↓↓↓	0	↓↓↓	↓↓↓	↓↓↓	0
Dartigues, *et al*[48]	1990	France	M+F: 143	Hos	FFQ						↓	↓
Jain, *et al*[49]	1990	Toronto, Canada	M+F: 839	Pop	DH		↓↓↓	0			↓	0
Kalandidi, *et al*[50]	1990	Athens, Greece Never-smokers	F: 91	Hos	FFQ		0	↓↓			0	↑?
Wu-Williams, *et al*[51]	1990	Northeast China Air pollution	F: 963	Pop	FFQ		0	↑				
Harris, *et al*[52]	1991	Oxford, UK	M: 96	Hos	FFQ	↓↓			0	↓↓	↓↓↓	↑
Candelora, *et al*[53]	1992	Florida, USA Never-smokers	F: 124	Pop	FFQ		↓↓↓	↓↓↓		↓?	↓↓↓	0
Forman, *et al*[54]	1992	Yunnan, China	M: 428		FFQ			0	↓↓↓	0		
Swanson, *et al*[55]	1992	Tin miners										
Alavanja, *et al*[56]	1993	Missouri, USA Nonsmokers	F: 429	Pop	FFQ		0	0			0	0
Mayne, *et al*[57]	1994	New York State, USA	M: 201	Pop	FFQ	↓↓↓[9]	0	↓			↓?	0
		Nonsmokers	F: 212			↓↓↓[9]	↓↓↓	↓↓			↓?	0

Continued...

Table 2. Continued

Study (ref)	Year	Location Population	No. of cases[d]	Study design[e]	Dietary assessment[f]	Vitamin A	Vitamin C	Total vitamin C	Vitamin E	Total vitamin E	Folate	Fiber
Mettlin, *et al* [7]	1979	Buffalo, NY, USA	M: 427	Hos	FFQ	↓?	0					0
Byers, *et al* [38]	1984											
Hinds, *et al* [15]	1984	Hawaii, USA	M: 261	Pop	DH	↓?		↓?				
Kolonel, *et al* [16]	1985	Multi-ethnic	F: 103			0		↑?				
Ziegler, *et al* [13]	1984	New Jersey, USA	WM: 736	Pop	FFQ	0						
Ziegler,*et al*[14]	1986	Whites & Blacks	WF: 860									
Dorgan, *et al* [39]	1993		BM: 269									
			BF: 86									
Samet, *et al* [40]	1985	New Mexico, USA	WM+F: 322	Pop	FFQ	↓↓↓						
		Whites & Hispanics	HM+F: 125			0						
Wu, *et al* [41]	1985	Los Angeles, CA, USA	W: 210	Com	FFQ	0						
		Whites										
Byers, *et al* [42]	1987	Western New York, USA	M: 296	Pop	FFQ	↓	↓	↓		↓		↓↓↓
			F: 154			0	0	0		0		↓
Gao, et al [43]	1987	Shanghai, China	F: 672	Pop	FFQ	↓?						
Pastorino, *et al* [44]	1987	Milan, Italy	F: 47	Hos	FFQ							
Fontham, *et al* [45]	1988	Louisiana, USA	M+F: 1253	Hos	FFQ		↓↓↓					
		Whites & Blacks										
Koo, *et al* [46]	1988	Hong Kong Chinese	F: 88	Com	FFQ							
		Never-smokers										
Le Marchand, *et al* [47]	1989	Hawaii, USA	M: 230	Pop	DH	↓↓↓	↓↓↓	↓↓↓			↓↓	↓↓
		Multi-ethnic	F: 102			↓↓	0	↑			↓↓	↓↓
Dartigues, *et al* [48]	1990	France	M+F: 143	Hos	FFQ							
Jain, *et al* [49]	1990	Toronto, Canada	M+F: 839	Pop	DH	0	0					0
Kalandidi, *et al* [50]	1990	Athens, Greece	F: 91	Hos	FFQ	0	↓	↓				
		Never-smokers										
Wu-Williams, *et al* [51]	1990	Northeast China	F: 963	Pop	FFQ							
		Air pollution										
Harris, *et al* [52]	1991	Oxford, UK	M: 96	Hos	FFQ							
Candelora, *et al* [53]	1992	Florida, USA	F: 124	Pop	FFQ	↓↓	↓↓↓					
		Never-smokers										
Forman, *et al* [54]	1992	Yunnan, China	M: 428		FFQ							
Swanson, *et al* [55]	1992	Tin miners										
Alavanja, *et al* [56]	1993	Missouri, USA	F: 429	Pop	FFQ		0	0	↑↑	↑		↓
		Nonsmokers										
Mayne, *et al* [57]	1994	New York State, USA	M: 201	Pop	FFQ					↓		
		Nonsmokers	F: 212							↓		

[a] To be included, studies had to assess diet in sufficient detail for the intake of several food groups and/or micronutrients to be evaluated. When several analyses of one study population have been published, results based on the largest number of lung cancer cases or deaths are used. [b] ↓↓↓ (and ↑↑↑ indicate inverse (and positive) associations with statistically significant trends. ↓↓ (and ↑↑) indicate inverse (and positive) associations with marginally significant trends or apparent trends that do not reach statistical significance. ↓ (and ↑) indicate inverse (and positive) associations with no evidence of a trend. ↓? (and ↑?) indicate inverse (and positive) associations with insufficient data presented to evaluate trend. 0 indicates no association. [c] Carotenoids, retinol, vitamin A, vitamin C, vitamin E, folate, and fiber refer to intake from foods. Total vitamin C and total vitamin E refer to combined intake from foods and supplements. [d] M: males; F: females; W: Whites; B: Blacks. [e] Hos: hospital-based; Pop: population-based; Com: community-based. [f] FFQ: food frequency questionnaire; DH: diet history. [g] Trends were seen for raw vegetables and fruits.

Strength of association and population preventive fraction

Since there is no generally accepted definition of adequate vegetable and fruit consumption, study populations are divided typically into quintiles, quartiles, or tertiles of intake in epidemiologic analyses. In both prospective and retrospective studies, smoking-adjusted RRs of lung cancer among those in the lowest quantile of intake have been approximately 1.3 to 2.0 times the risks of those in the highest quantile of intake.[26,27,87,88] In recent studies in North America, RRs between extreme quartiles or tertiles have been 1.4 for vegetables (New Jersey men and women);[39] 1.6 for raw vegetables and fruits (New York State men and women);[57] 1.7 for vegetables (men and women in Toronto, Canada);[49] 1.7 for vegetables and fruits (women in a Los Angeles retirement community, but no protective effect in men);[32] and 2.0 for vegetables and fruits (Iowa women).[37] Reviews and articles often point out that this 30 to 100 percent increase in risk is probably an underestimate because of imprecise assessment of exposure.[27,87,88] However, it also may be an overestimate due to uncontrolled confounding by smoking and possibly other exposures, such as environmental smoke and pollution. In addition, the tendency to emphasize the strongest association detected in a particular study, among the several calculated for vegetables, fruits, their subgroups, carotenoids, *etc.*, exaggerates the strength of the underlying association.

A 30 to 100 percent increase in lung cancer risk associated with the lowest quartile of vegetable and fruit intake, compared with the highest quartile, has important public health implications. If increased vegetable and fruit intake is truly protective, and the relative reduction in risk is proportional to intake, then 10 to 33 percent of potential lung cancer cases could be prevented if all individuals in the population were to adopt the levels of vegetable and fruit intake characteristic of the highest quartile.

Potential mechanisms

While it is biologically plausible that a diet enriched with vegetables and fruits might reduce lung cancer risk, the specific mechanisms need to be elucidated. Experimental mutagenesis and carcinogenesis in animals can be inhibited by a large number of compounds from edible plants, including carotenoids, polyphenols, thiols, trace metals, terpenes, tocopherols, and degradation products of glucosinolates.[84,89] Within each of these groups are several compounds that may exert their chemopreventive action by more than one biologic mechanism.[89] For example, carotenoids are not only antioxidants and free radical quenchers,[90] but also modulate the immune system[91] and affect gap junction communication.[92] In addition, recent research suggests that β-carotene can be metabolized to retinoic acid by both central and excentric cleavage mechanisms.[93] Retinoic acid is believed to function as a key regulator of gene expression, morphogenesis, and growth in vertebrate embryos. These observations suggest that carotenoids, as well as vegetables and fruits, may have multiple, complex mechanisms of action.

Antioxidant micronutrients

The recent excitement about β-carotene focused attention on other micronutrients that might function as antioxidants. Smoking, the dominant cause of lung cancer, exposes lipids, proteins, and nucleic acids in the lungs to oxidative damage.[94,95] Other antioxidant micronutrients include vitamin E, a fat-soluble vitamin known to prevent lipid peroxidation; vitamin C, a water-soluble vitamin with several important functions; and selenium, a trace mineral essential for several enzymes, including glutathione peroxidase. Lung cancer has been discussed in two recent reviews[96,97] of antioxidant micronutrients and cancer.

Usual vitamin E intake can be measured best by α-tocopherol levels in the blood or by a history of vitamin E supplementation. Relying on dietary assessment methods to classify individuals is problematic since the intake of fats and oils, which are rich in vitamin E, is difficult to discern and quantify. Further, accurate data on the vitamin E content of foods is limited by the frequent substitution of fats and oils in commercial products. Of the six prospective studies that have measured α-tocopherol in prediagnostic blood samples and accrued at least 25 lung cancers (Table 3), only three[20,63,71] found inverse associations. Only in the Washington County cohort was the trend statistically significant and as strong as that seen for serum β-carotene.[20] The RR for those in the lowest quintile of serum α-tocopherol levels, relative to the highest quintile, was 2.5, and not altered by adjustment for smoking or serum cholesterol. In a disconcerting report, Wald *et al*[67] demonstrated that serum α-tocopherol levels were reduced in lung cancer patients up to three years prior to diagnosis, presumably as a metabolic consequence of the disease. While time trends were not evident in the Washington County results, they cannot be ruled out for the other two cohorts[63,71] with nonsignificant protective effects for vitamin E, especially since lung cancer mortality, not incidence, served as the outcome. Four studies have assessed total vitamin E intake, including contributions from supplements (Tables 1 and 2). Protective effects were restricted to men in one[42] and to women in a second[32] and were absent in a third.[56] However, Mayne and colleagues,[57] in a case-control study con-

ducted in nonsmokers, observed a reduced risk of lung cancer for vitamin E supplement users, relative to nonusers, in both genders (RRs = 0.5-0.6). The inverse association was statistically significant and not seen for other vitamin supplements, but trends by dosage and duration of use could not be evaluated.

Recently, vitamin C has been hypothesized to prevent lung cancer.[98] Vegetables, fruits, fortified foods, and vitamin supplements are the major sources of vitamin C in the diet. Five prospective[8,12,30,35,36] (Table 1) and four retrospective[38,45,49,53] (Table 2) studies have developed indices of vitamin C intake from vegetables and fruits; the contribution of vitamin supplements was assumed to be negligible. In three[30,45,53] of these nine studies, the inverse trends with lung cancer risk were significant. However, comparable trends were noted with total fruit intake, and were generally stronger than those with citrus fruit.[30,45] In four[8,33,35,38] of the nine studies, dietary vitamin C was not related to lung cancer risk. Of the two prospective and five retrospective studies that integrated supplemental vitamin C information, and thus were able to classify individuals more accurately, no inverse association was observed in two;[37,56] and differential effects in men and women were noted in four.[15,32,42,47] Of these seven studies, five compared total vitamin C intake with vegetable and fruit consumption; in four, more consistent[15,47] and/or stronger[37,50] inverse associations were seen with a food group. Only one cohort study[63] assayed micronutrients at the time of blood collection and thus was able to measure vitamin C since vitamin C degrades rapidly in blood. Plasma vitamin C was not predictive of subsequent lung cancer mortality.[63]

Since the selenium content of an individual food is determined primarily by soil selenium levels, assessment of selenium status is accomplished best by biochemical, not dietary, measures.[99] The six prospective studies that measured prediagnostic serum selenium in at least 25 individuals who were diagnosed with or died from lung cancer (Table 3) have found positive,[20] negative,[70,73] and null[65,75,77] associations. Divergent results also were reported recently by two prospective studies[76,78] which measured selenium in toenails (Table 3), thus integrating exposure over several months. However, the largest of the blood[73] and toenail[76] studies, and the only two analyses with statistically significant trends, identified inverse relationships; the smoking-adjusted RRs for men in the highest selenium quintile, relative to the lowest quintile, were 0.3 and 0.5, respectively. In neither study was there evidence that preclinical disease explained the associations. Inverse associations may have been apparent because Finland[73] and Holland[76] where these studies were carried out, had low and intermediate levels of selenium intake, respectively. Reported blood and tissue levels in both countries were substantially below US levels and may have precluded optimal enzyme activity by glutathione peroxidase and/or other selenium-dependent enzymes in sizable proportions of the populations.[73,76,100] However, other plausible mechanisms, whereby high concentrations of selenium should be anticarcinogenic, independent of glutathione peroxidase activity, have also been proposed.[101] Although it has been suggested that the protective effect of selenium may be restricted to men,[102] a significant inverse trend with toenail selenium was observed among the women in the Dutch cohort.[76]

Although individual observational studies have suggested a protective role for vitamin E, vitamin C, and selenium in lung carcinogenesis, the totality of the evidence at present for any one of these antioxidant micronutrients is not convincing. While it is plausible that the biologic interaction of antioxidants is complex, reasonable models for integrating antioxidant capacity have not yet been developed and evaluated.

Folic acid

Krumdieck and others[103,104] have proposed that chemicals in cigarette smoke produce a localized deficiency of folic acid in the bronchial epithelium, thus rendering it more susceptible to neoplastic transformation, since folic acid is essential for nucleic acid synthesis and repair. The only observational study to evaluate folate intake found nonsignificant inverse trends with lung cancer risk in men and in women, but they were less pronounced than those with total vegetable or dark-green vegetable consumption.[47] In a correlational analysis, plasma folate was lower in smokers with lung metaplasia than in smokers without metaplasia,[105] but may have been simply a biomarker of intensity of cigarette use or of disease progression rather than an independent determinant of cancer susceptibility. No prospective study has investigated the importance of prediagnostic blood folate levels in the development of lung malignancy.

Total fat, saturated fat, and cholesterol

Correlation studies

Nearly 20 years ago, Carroll and Khor[106] observed a strong positive correlation between lung cancer mortality of 40 countries and *per capita* fat availability. With one exception,[107] similar observations were made in subsequent and more detailed analyses of international mortality rates and updated food disappearance data.[108,109] Wynder *et al*[108] reported that the positive association between dietary fat and lung cancer mortality was independent of smoking habits and nonfat calories. Xie and coworkers[109] concluded that the effect of dietary fat

Table 3. Prospective studies of blood micronutrient levels and lung cancer[ab]

Study (ref)	Year	Location Population	No. of cases[c]	Years of follow-up	β-carotene	Vitamin A	Vitamin E	Vitamin C	Selenium
Stahelin, *et al*[18]	1984	Basel, Switzerland	M: 68	12-14	↓↓↓	↓[d]	↓	0	
Stahelin, *et al*[63]	1991								
Stahelin, *et al*[64]	1991								
Nomura, *et al*[19]	1985	Hawaii, USA	M: 74	~10	↓↓↓	0	0		0
Nomura, *et al*[65]	1987	Japanese							
Menkes, *et al*[20]	1986	Washington County, MD, USA	M+F: 99	9	↓↓↓	0	↓↓↓		↑↑
Wald, *et al*[66]	1986	London, UK	M: 50	3-10	↓↓↓	0	0		
Wald, *et al*[67]	1987								
Wald, *et al*[68]	1988								
Friedman, *et al*[69]	1986	San Francisco-Oakland, CA, USA	M+F: 151	7-14		0			
Virtamo, *et al*[70]	1987	Finland 55+ years old	M: 38	9					↓?
Connett, *et al*[71]	1989	22 centers in USA	M: 66	10	↓↓	0	↓		
Knekt, *et al*[72]	1988	Finland	M: 144	5-9	0	↓?	↑?		↓↓↓
Knekt, *et al*[73]	1990								
Knekt, *et al*[74]	1990								
Criqui, *et al*[75]	1991	10 centers in USA	M+F: 27	8.5		0			0
Van den Brandt, *et al*[76]	1993	Netherlands	M: 285	3					↓↓↓[e]
		55+ years old	F: 32						↓↓↓[e]
Kabuto, *et al*[77]	1994	Japan	M+F: 77	11-13					0
Garland, *et al*[78]	1995	USA	F: 47	3.5					↑↑[e]

[a] Only analyses with at least 25 lung cancer cases or deaths are included. When sequential analyses of one cohort have been published, results based on the largest number of lung cancer cases or deaths are used.

[b] ↓↓↓ (and ↑↑↑) indicate inverse (and positive) associations with statistically significant trends. ↓↓ (and ↑↑) indicate inverse (and positive) associations with marginally significant trends or apparent trends that do not reach statistical significance. ↓ (and ↑) indicate inverse (and positive) associations with no evidence of a trend. ↓? (and ↑?) indicate inverse (and positive) associations with insufficient data presented to evaluate trend. 0 indicates no association.

[c] M: males; F: females.

[d] Only observed in men 60+ years of age.

[e] Selenium was measured in toenails.

could be attributed to animal fat but not to vegetable oils. Both groups proposed that dietary lipids could explain, in part, international differences in lung cancer rates. To that end, Taioli *et al*[110] compared the smoking and dietary habits of northern and southern Italians and related the data to lung cancer mortality rates. They concluded that, adjusted for smoking, the lower incidence of lung cancer among southern Italians might be attributed to a dietary pattern characterized not only by more frequent consumption of vegetables and fruit but also by a lower intake of both saturated and polyunsaturated fat.

Retrospective studies

Researchers in Hawaii conducted a series of analytic epidemiologic studies[111-114] to explore the relation of dietary lipids and lung cancer risk. Initially, the focus was on dietary cholesterol, which had been identified as a potential risk factor in an early ecologic study conducted among the major ethnic groups in Hawaii.[115] The first[111] of three case-control studies indicated a positive association between dietary cholesterol and lung cancer risk within a multi-ethnic population (Table 4). The association appeared to be confined to men, but relatively few women were studied. In a subsequent study employing a quantitative diet history questionnaire specifically designed to assess cholesterol and fat intake,[113] dietary cholesterol again was associated directly with lung cancer risk. The effect was restricted to men, heavy smokers, and cases with squamous cell carcinoma. The investigators also noted a threshold effect, that is, risk was elevated about twofold in the second through fourth quartiles of intake. As noted by the investigators, the effects of dietary fat (total, saturated, and unsaturated) were indistinguishable from those of cholesterol and could not be disentangled. In a subsequent analysis of foods and food groups,[114] the importance of fat, specifically animal fat, was emphasized. Smokers, particularly men, who had high intakes of foods rich in animal fat (*e.g.*, dairy foods, some processed meats) had increased lung cancer risk.

Other case-control studies[42,49,56,62] also have suggested an association of dietary lipids and lung cancer risk. Byers *et al*[42] observed a positive but statistically nonsignificant relation between cholesterol and total fat and risk

of lung cancer among men, but not women. Canadian investigators[49] noted positive associations for cholesterol and saturated and total fat among both men and women. The fat effect, however, disappeared after adjustment for dietary cholesterol. In marked contrast to Goodman's study in Hawaii,[113] the cholesterol effect did not vary by gender or smoking status and was stronger for lung adenocarcinoma than squamous cell lung cancer. In a study of 281 male lung cancer patients in Kerala, South India,[62] lung cancer risk was elevated two- to 12-fold among frequent consumers of eggs, dairy products, and meat. The risk estimates, however, did not appear to be adjusted for the protective effects of vegetables and fruits. While all six case-control studies that included smokers considered smoking status,[42,49,62,111,113,114] several investigators have expressed concern that dietary findings may reflect residual confounding and an inability to control for smoking intensity or other smoking characteristics.

Interestingly, one of the most pronounced associations of dietary fat and lung cancer risk was observed in a study of nonsmoking Missouri (USA) women.[56] Risk increased with increasing levels of total fat; the effect was attributed to saturated fat. The RR was sixfold greater for the highest quintile of consumption compared with the lowest quintile and was even more pronounced among women with adenocarcinoma. This and most previous case-control studies have been limited by relatively low response rates (often less than 60 percent) and considerable reliance on proxy interviews. Response rate was excellent in a study of Greek women that included 91 case-control pairs of never-smokers.[50] In this population of women consuming diets rich in monounsaturated fats, risk of lung cancer was not related to consumption of meat, dairy products, fats, or oils. Other case-control studies with large numbers of nonsmoking women are not informative with respect to the role of dietary fat.[43,51] These studies were conducted in mainland China where intake of fat, saturated fat, and cholesterol is very low. One would not expect necessarily to see an association in a population with uniformly low intakes. Studies of women in China and Singapore suggest an interesting, albeit tangential, link between fat and lung cancer risk. In three studies,[9,43,51] risk of the disease was related directly to exposure to cooking oil vapors resulting from stir-frying.

Prospective studies

Relatively few prospective studies of dietary fat and lung cancer have been conducted; and most were so limited by sample size that critical issues such as effect modification by gender, smoking status, and histologic type could not be addressed. In a cohort of Japanese Hawaiian men, Heilbrun and colleagues[112] assessed cholesterol intake using the 24-hour diet recall method. In contrast to results of a previous case-control study conducted in Hawaii,[111] they found no relation between cholesterol intake and subsequent risk of lung cancer (Table 4). A single 24 h recall, however, probably does not provide a representative estimate of usual cholesterol intake. In a prospective study of Seventh-day Adventists in California which yielded 61 incident cases of lung cancer,[34] risk of the disease was elevated among individuals who frequently consumed meat, especially poultry. Both fat and saturated fat, but not cholesterol, were associated weakly with lung cancer risk in a cohort of Finnish men.[116] However, the adverse effect of saturated fat, and presumably total fat, was attributed largely to confounding by smoking. Shekelle *et al*[117] reported a direct relation of dietary cholesterol and lung cancer risk among men living in Chicago. Only one prospective study of dietary lipids and lung cancer risk has focused on women. A recent study of postmenopausal women in Iowa,[118] indicated that intake of dietary fat, saturated fat, and cholesterol were not predictive of lung cancer risk.

The positive association of dietary cholesterol and lung cancer risk has not been reflected in studies of serum cholesterol levels. On the contrary, in a number of investigations of all cancers,[119-122] serum cholesterol was related inversely to risk of lung cancer. Several interpretations for the inverse association have been proposed, including a direct causal link, low cholesterol serving as a marker for the true risk factor (possibly low levels of serum β-carotene),[119] or low cholesterol values reflecting disease effects.

Interpretation and potential mechanisms

More than 50 years ago, dietary fat was identified as a tumor promotor in experimental animals.[123] Ecologic studies later suggested that a variety of dietary lipids might be involved in the etiology of human lung cancer. With some notable exceptions, several analytic epidemiologic studies have provided support for the hypothesis that dietary lipids are associated positively with lung cancer risk. There are obvious inconsistencies, however, particularly regarding the magnitude of the associations. There is disagreement as to whether the associations are modified by gender, smoking status, and histologic type of lung cancer. The component(s) of dietary fat responsible for the relationship with risk has not been identified. The relevant variables (*e.g.*, cholesterol, total and saturated fat) tend to be highly correlated and difficult to disentangle. Few investigators have attempted to control for intake of energy, carotenoids, fruits or vegetables. However, in the studies where these variables were considered, the lipid effects were not explained by confounding.

It is biologically plausible that dietary lipids may promote lung carcinogenesis although, as with vegetables and fruits, the precise mechanisms are unclear. Dietary

Table 4. Studies of dietary fat, saturated fat, cholesterol, and lung cancer[a]

Study (ref) Year	Location Population	No. of cases[b]	Relative risks for high *cf* low-intake categories		
			Fat	Saturated fat	Cholesterol
Retrospective studies					
Hinds, *et al*[111] 1983	Hawaii,USA Multi-ethnic	M: 261 F: 103	— —	— —	2.3 1.2
Byers, *et al*[42] 1987	Western New York, USA	M: 296 F: 154	2.0 1.0	— —	1.4 0.9
Goodman, *et al*[113] 1988	Hawaii, USA Multi-ethnic	M: 226 F: 100	2.2 0.9	2.1 1.4	2.2 0.9
Jain, *et al*[49] 1990	Toronto, Canada	M+F: 839	1.3	1.3	1.5
Alavanja, *et al*[56] 1994	Missouri, USA Nonsmokers	F: 429	—	6.1	—
Prospective studies					
Heilbrun, *et al*[112] 1984	Hawaii, USA Japanese-American	M: 109	—	—	1.0
Knekt, *et al*[116] 1991	Finland	M: 117	1.6	1.5	1.0
Shekelle, *et al*[117] 1991	Chicago, IL, USA	M: 57	—	—	1.9[c]
Wu, *et al*[118] 1994	Iowa, USA 55+ years	W: 212	0.8	0.9	0.9

[a] Studies which focused primarily on food groups are not included.
[b] M: Males; F: females.
[c] Risk associated with each 500 mg increment in dietary cholesterol.

lipids have been postulated to affect carcinogenesis via effects on the immune system, gap junction-mediated intercellular communication, endocrine processes, and cell proliferation.[124] Recently, Shields *et al*[125] identified a number of mutagens and carcinogens in the volatile emissions of cooking oils, particularly unrefined oils used in stir-frying, that may explain the elevated risks associated with this cooking method in Asian women.

Independence and interrelationships of dietary effects

Adequate control of confounding by smoking is crucial in observational studies of diet and lung cancer. Several studies have demonstrated that consumption of vegetables, fruits, and carotenoids is higher in nonsmokers than in current smokers, and in smokers, is related inversely to smoking intensity.[33,126] Vegetable, fruit, and carotenoid intake also may be associated inversely with smoking duration and recency. Thus, those lung cancer studies that only considered whether subjects were current, ex-, or never smokers may have generated inflated estimates of the protective effect of vegetables, fruits, and carotenoids. Several studies[14,37,47] have confirmed that confounding is inadequately controlled by this approach. Environmental smoke also may present problems. Shibata and colleagues[33] pointed out that, among men with comparable smoking histories (current, ex-, or never), the wife's smoking history was related significantly and inversely to her husband's carotenoid intake. Nonetheless, in several recent analyses of nonsmokers, passive smoking did not confound the lung cancer/vegetable and fruit relationships.[50,56,57] Studies of blood nutrient levels and lung cancer present even more of a challenge than dietary studies since blood levels of carotenoids, vitamin C, and folate appear to be lower in smokers than in nonsmokers with similar nutrient intake.[105,127,128] The published analyses of dietary fat, saturated fat, cholesterol, and lung cancer risk have adjusted for smoking, but it is not clear how adequately confounding was controlled. Thus, if smokers tend to consume high-fat diets, estimates of the lipid associations also may be inflated.

Many of the studies of the influence of dietary fat, saturated fat, and cholesterol intake on lung cancer risk have adjusted for measures of vegetable, fruit, and carotenoid intake.[49,56,113,114,116,119] However, few of the studies of vegetable, fruit, and carotenoid intake have adjusted for macronutrients.[15,42,49,81] One reason was that their dietary assessment instruments were focused on vegetables and fruits and could not be used to measure fat and cholesterol intake; another was that vegetable and fruit findings have predated the lipid findings. The two dietary associa-

tions seem to be independent, in that neither is explained completely by the other. None of the lung cancer studies that have found effects for both vegetables and fruits and lipids have clarified their intercorrelation, or their interaction in determining risk. Analyses of dietary data from two nationally representative US surveys have indicated that vegetable, fruit, and carotenoid intake are not correlated highly with fat, saturated fat, and cholesterol intake.[28,129,130,131] Thus, it should be possible to disentangle their effects on lung cancer risk.

Intervention trials

Historical perspective

As reviewed earlier, observational studies have demonstrated consistently that individuals who consume diets rich in vegetables, fruits, and carotenoids are at reduced risk of lung cancer. This finding, along with data indicating that retinol, retinoids, and β-carotene inhibit carcinogenesis in animal experiments, led Peto and coauthors[11] to speculate that "long-term randomized intervention studies with β-carotene might be worthwhile on almost any category of persons at high enough risk of cancer for several dozen occurrences, recurrences or progressions to be anticipated in a practicable sized study group within a few years." Subsequently, several intervention trials involving β-carotene in populations at risk for lung cancer were implemented (Table 5). Some trials chose to add retinol to the β-carotene supplement, for several reasons. First, retinol and retinoids had been shown to be effective at inhibiting carcinogenesis in numerous animal models.[5] Second, administration of retinol presumably would meet vitamin A requirements and thus allow for greater absorption and bioavailability of intact β-carotene. Third, the combination of supplemental β-carotene plus retinol was more effective than β-carotene alone in reducing micronucleated buccal mucosal cells, an indicator of genotoxic damage, in populations at very high risk of oral cancers.[145]

Lung cancer prevention trials can use premalignant endpoints and/or incident lung cancer as the primary outcome. Those that use cancer as the outcome consist of primary prevention trials, in which the participants are at risk for lung cancer but have never had the disease, and secondary prevention trials, also known as adjuvant chemoprevention trials, in which the goal is to prevent the development of lung cancer following the diagnosis and treatment of a first malignancy. Primary prevention trials typically enroll 20,000 to 30,000 participants with multiyear interventions. These trials are thus extraordinarily expensive and difficult and require many years to complete. Secondary prevention trials are less expensive, require smaller sample sizes, but may have limited generalizability. Intervention trials using premalignant endpoints as the primary outcome are also less costly and provide data in a more timely fashion than trials with cancer as the outcome. However, intermediate endpoints for lung cancer, which usually are based upon visual evaluation of cells obtained from sputum, bronchial washings, or bronchial biopsy, have not been validated as being predictive of lung cancer, and thus must be interpreted with caution. Results of all three types of trials – primary prevention, secondary prevention, and premalignant endpoints – are now available for lung cancer.

Premalignant endpoints

The Tyler (Texas) Chemoprevention Trial[132] randomized 755 asbestos workers to receive either β-carotene plus retinol or a placebo, to see if the nutrient combination could reduce the prevalence of atypical cells in sputum. After a mean intervention period of 58 months, there was no difference in the two groups.[133] Synthetic retinoids also have been tested in intervention trials using bronchial metaplasia as an endpoint. As reviewed elsewhere,[146] retinoids have not been effective with regard to bronchial metaplasia in two randomized trials. Supplemental β-carotene, however, significantly reduced micronuclei counts in lung sputum in a 14-week, randomized, placebo-controlled intervention trial involving 114 heavy smokers.[134] Micronuclei are indicative of DNA damage and thus may provide a marker of early stages in the carcinogenic process; however, the relationship between micronuclei and lung carcinogenesis is speculative at present.

Results are available from one other randomized trial based on bronchial metaplasia. Heimburger *et al*[135] reported that the combination of folic acid plus vitamin B_{12} had significantly reduced atypical bronchial squamous metaplasia after four months of supplementation in 73 male heavy smokers. While these results are promising, the sample size was small and the statistical analysis of the data has been questioned.[146]

Malignant endpoints

Only one primary prevention trial of lung cancer focusing on nutrients has been completed (please refer to the addendum on p. 177). The trial involved 29,133 males from Finland, aged 50-69 years, who were heavy cigarette smokers at entry (averaging one pack/day and 36 years of cigarette use).[136, 137] The study design was a two-by-two factorial, with participants randomized to receive either supplemental α-tocopherol (50 mg/day), β-carotene (20 mg/day), the combination, or placebo for five to eight years. These doses represented a fivefold excess over the median dietary intake of α-tocopherol in this population (10.3 mg), and more than a tenfold excess over the median intake of β-carotene (1.7 mg).[136] Vitamin

Table 5. Chemoprevention trials relevant to nutrition and lung cancer

Study (ref) Year	Population	Daily intervention	Total subjects	Endpoint	Result
Premalignant endpoints					
McLarty, *et al*[133] 1995	Male asbestos workers	50 mg β-carotene 25,000 IU vitamin A[b]	755	Sputum atypia	OR = 1.24 (CI = 0.78-1.96)
Van Poppel, *et al*[134] 1992	Male smokers	20 mg β-carotene	114	Sputum micronuclei	27% decrease (CI = 9-41%)
Heimburger, *et al*[135] 1988	Male smokers with metaplasia	10 mg folate 500 ug B_{12}	73	Sputum atypia	Cytology score improvement $P=0.02$
Primary prevention - completed					
ATBC[137] 1994	Finnish male smokers	20 mg β-carotene 50 mg vitamin E	29,133	Lung cancer	β-c: RR = 1.18 (CI = 1.03-1.36) Vit E: RR = 0.98 (CI = 0.86-1.12)
Physicians' Health Study[139] 1989	Male physicians	50 mg β-carotene[b] 325 mg aspirin[b]	22,071	Cancer, coronary heart disease	*
CARET[138] 1992	Smokers/ asbestos workers	30 mg β-carotene 25,000 IU vitamin A	18,314	Lung cancer	RR = 1.28 (CI = 1.04-1.57)*
Primary prevention - ongoing					
Women's Health Study[140] 1992	Female nurses	50 mg β-carotene[b] 400 IU vitamin E[b] 100 mg aspirin[b]	40,000	Cancer, coronary heart disease	*
Heart Protection Study[141] 1994	High risk coronary heart disease (U.K.)	20 mg β-carotene 600 mg vitamin E 250 mg vitamin C	20,000+	Cancer, coronary heart disease	
Secondary prevention - completed					
Pastorino[142] 1993	Stage I non-small cell lung cancer patients	300,000 IU vitamin A	307	Second cancer	Longer time to second cancer $P = 0.045$
Secondary prevention-ongoing					
EUROSCAN[143] 1991	Oral, larynx, lung cancer patients	300,000 IU vitamin A 600 mg N-acetylcysteine	2,000	Second cancer	
Mayne[144] 1992	Oral, pharynx, larynx cancer patients	50 mg β-carotene	480	Lung cancer, second cancer	

[a] OR = odds ratio; CI = 95% confidence interval; RR = relative risk; β-c = β-carotene; Vit E = Vitamin E.
[b] The dosage listed was taken every other day. All others are daily dosages.
* Please refer to the addendum on p. 177.

E supplements did not affect the incidence of lung cancer (RR = 0.98).[137] Unexpectedly, participants receiving β-carotene (alone or in combination with vitamin E) had significantly higher lung cancer incidence (RR = 1.18; 95 percent confidence interval (CI) = 1.03-1.36) and total mortality (RR = 1.08, CI = 1.01-1.16) than participants receiving the placebo. Notably, however, there were inverse associations between β-carotene intake and serum β-carotene concentrations, as measured at baseline, and lung cancer incidence in the unsupplemented group, consistent with other observational epidemiologic studies. The incidence rates per 10,000 person-years for the highest and lowest serum quartiles were 43.1 and 53.3, and for the highest and lowest dietary quartiles were 39.9 and 47.9, respectively.

The unexpected finding of a modest increase in the risk of lung cancer with β-carotene supplementation could be a chance finding. While there are other ongoing lung cancer prevention trials (Table 5), they all differ with regard to key design features so that none may be able to confirm or refute the β-carotene results of the Finnish trial. The Carotene and Retinol Efficacy Trial (CAR-

ET),[138] an ongoing, multicenter, lung cancer prevention trial, is utilizing a combination intervention of β-carotene plus retinol, in the absence of a factorial design, and includes both asbestos workers and smokers, some of whom are women. The Physicians' Health Study,[139] another large β-carotene intervention trial, involving 22,000 US male physicians, is not comparable to the Finnish trial in that only 10 percent of the cohort were current smokers at entry.[147] A trial that investigated the effects of selected combinations of nutrients on esophageal and gastric cancer in China[148] had only 31 lung cancer deaths, and thus limited statistical power. Nonetheless, the RR of lung cancer mortality was 0.55 (CI = 0.26-1.14) among those receiving the combination of 15 mg β-carotene, 30 mg α-tocopherol, and 50 μg selenium per day.[148]

In contrast to the disappointing results of the Finnish trial are recent results of a secondary prevention trial in patients cured of a prior, early-stage lung malignancy.[142] These patients have a very high risk for developing a new malignancy in the lung or elsewhere in the upper aerodigestive tract; therefore, prevention of secondary malignancies is an efficient study design for examining chemopreventive efficacy. The 307 patients treated with curative surgery for Stage I, non-small cell lung cancer were randomized to receive very high doses of retinol palmitate for 12 months or to be observed. After a median follow-up of nearly four years, 18 patients in the supplemented group *cf* 29 patients in the control group developed second primary tumors. A statistically significant difference ($P = 0.045$, log-rank test) in favor of the supplemented group was observed in the time to new primary tumors in the combined sites of interest (lung, head and neck, and bladder – all tobacco-related malignancies).

Interpretation of intervention trials

While the unexpected result of the Finnish trial may be due to chance, many other possibilities should also be considered: (i) β-carotene/carotenoids may lack cancer-protective effects but may serve as markers for other protective dietary factors or correlated lifestyles; (ii) carotenoids other than all-*trans* β-carotene might be protective; (iii) β-carotene/carotenoids might be protective, but only when administered in a natural matrix allowing for synergistic interactions with other antioxidants and phytochemicals; (iv) β-carotene/carotenoids might be protective if present early in the carcinogenic process; (v) β-carotene/carotenoids might be protective, but only if administered over a number of years; (vi) dietary levels of β-carotene/carotenoids could be beneficial, whereas pharmacologic levels could be beneficial, neutral, or deleterious, depending upon baseline nutritional status and other factors.

As for the latter possibility, the dose of β-carotene used in the Finnish trial (20 mg/day) was not particularly high compared with doses used in other cancer prevention trials, which range up to 50 mg/day. However, the resulting serum response was dramatic. Median β-carotene levels rose from 0.17 mg/L at baseline to 3.0 mg/L at three years.[137] In contrast, median β-carotene levels in participants receiving 50 mg/day in a skin cancer prevention trial rose from 0.18 mg/L at baseline to only 1.7 mg/L at three years.[149]

There has been much speculation regarding the results of the Finnish trial. Possible explanations include adverse reactions with ethanol[150] and pro-oxidant effects of β-carotene.[151] Adverse effects of β-carotene on the absorption or utilization of other lipid-soluble substances (*e.g.*, other carotenoids, tocopherols, and phytochemicals) also should be considered. For example, intake of α-carotene and of lutein is associated inversely with lung cancer risk.[81,82] If pharmacologic doses of β-carotene adversely affected bioavailability of these two carotenoids, this potentially could increase cancer risk. As reviewed elsewhere,[152] supplemental β-carotene has been reported to decrease blood and tissue levels of α-tocopherol[153,154] and lutein[155,156] in small studies, although larger studies indicated that supplemental β-carotene actually increased blood levels of α-carotene[157,158] and lycopene,[158] and did not affect blood levels of α-tocopherol[159,160] or lutein/zeaxanthin.[158] One explanation for the finding that supplemental β-carotene reduced lutein in short-term, but not longer-term, studies is the dosing protocol. In the short-term studies, β-carotene was administered concurrently with lutein,[156] or with the lunch and dinner meals;[155] thus, the likelihood of direct competition for absorption was maximized. In the clinical trials, however, subjects generally took one supplement daily or even every other day,[139,140] often with breakfast, when relatively few lutein-rich green leafy vegetables are consumed, thus reducing the likelihood of competition for absorption. Additional research is needed in the area of interactions between carotenoids and other nutrients and phytochemicals, to aid in our understanding of health effects of carotenoid supplements and to provide data supporting rational recommendations regarding protocols for future trials.

Our lack of knowledge about mechanisms of action of β-carotene in carcinogenesis, coupled with the enormous expense of conducting β-carotene primary prevention trials, raises the question of whether initiation of these trials in the 1980s was premature. It has been suggested that failure to start these trials at that time might have precluded their implementation as the 'window of opportunity' for placebo-controlled trials of commercially available antioxidant micronutrients appeared to be closing,[161] at least in developed countries. Somewhat para-

doxically, the results of the Finnish trial may have dampened the enthusiasm for antioxidant supplementation in the general population, and thus provided an opportunity to continue the next generation of chemoprevention trials.[161]

In summary, nutrient supplement trials with lung premalignancy or malignancy as the outcome have had mixed results. The largest completed trial indicates that five to eight years of supplementation with β-carotene does not reduce lung cancer incidence in Finnish males who were heavy smokers at entry. Effects of supplemental β-carotene in lung cancer prevention in other populations are not yet known. In particular, data evaluating the efficacy of nutrient supplements for lung cancer prevention in women are needed, as the published studies used predominantly[142] or exclusively[133,134,135,137] men. An ongoing trial of supplemental β-carotene and vitamin E in 40,000 US women[140] will help to rectify the lack of information in this area (please refer to the addendum on p. 177). Thus, at present, the potential of supplemental nutrients for the prevention of lung cancer remains unknown.

Summary and conclusions

Since the last major reviews of diet and lung cancer, published around 1990, the consistency of the epidemiologic evidence and the simplicity of the interpretation have been eroded. Observational studies of diet and lung cancer, both prospective and retrospective, continue to suggest strongly that increased vegetable and fruit intake is associated with reduced risk in men and women; in various countries; in smokers, ex-smokers, and never-smokers; and for all histologic types of lung cancers. Prospective studies of blood β-carotene levels, arguably the best biomarker of vegetable and fruit intake, indicate that low levels are predictive of increased lung cancer incidence. However, based on the remarkable results of the randomized, placebo-controlled trial in Finnish male smokers, in which lung cancer incidence was increased significantly among the men receiving β-carotene supplements, protection by β-carotene no longer provides a simple explanation of the observational epidemiology. If β-carotene does reduce the risk of lung cancer, which the Finnish trial cannot rule out, then the dosage, duration of use, chemical formulation, method of administration, and/or subpopulation are critical.

Increased intake of other individual carotenoids, specifically α-carotene and lutein, has been associated with reduced lung cancer risk in two observational studies. Many other phytochemicals theoretically could be involved in lung carcinogenesis; but limited information on their distribution in the food supply and the lack of biomarkers have frustrated their evaluation in epidemiologic investigations. While in most observational studies of lung cancer, diets high in vegetables and fruits are protective, specific studies and specific subpopulations have failed to corroborate the relationship; and the strength of the association varies widely. This inconsistency in the literature, although limited in scope, has continued over time and emphasizes our lack of understanding of the underlying etiology for these findings.

Several observational epidemiologic studies, both prospective and retrospective, have suggested that diets high in fat, saturated fat, and cholesterol may increase the risk of lung cancer and that the effect is not mediated through vegetable and fruit intake. Underlying mechanisms are not clear. Although the relationship is not yet established, it merits investigation in future work. Since β-carotene can function as an antioxidant, other micronutrients with this potential, specifically vitamins E and C and selenium, also have been proposed to reduce lung cancer risk. However, the totality of the epidemiologic evidence is not, at present, persuasive for any one of these micronutrients.

Although modifying diet may seem easier than modifying smoking habits, the decrease in lung cancer risk associated with increased vegetable and fruit intake is, at most, twofold, while quitting smoking causes approximately a 20-fold drop in risk. For those wishing to enhance their defenses against environmental smoke and pollution, radon, and occupational exposures linked to lung cancer, increased vegetable and fruit intake may be prudent. Certainly such dietary modification is unlikely to be harmful. Introducing a variety of vegetables and fruits into the diet, and the potentially beneficial nutrients and phytochemicals concentrated within them, may reduce the risk of lung cancer, and possibly the risk of other cancers and chronic diseases as well.

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Addendum

On 18 January 1996, the US National Cancer Institute held a press conference releasing major findings from two of the intervention trials mentioned in this review: CARET[138] and the Physicians' Health Study.[139] CARET investigators announced that the intervention component of their trial was being terminated nearly 2 years early because interim analyses indicated that lung cancer incidence was unlikely to be reduced in the participants taking the combination of β-carotene and retinol by the scheduled end of the study. Moreover, there was a substantial possibility that the supplements might be harming subjects, consistent with the findings of the ATBC Trial discussed in this manuscript.[136, 137] In CARET, the relative risk estimate for lung cancer was 1.28, with a 95 percent confidence interval (CI) of 1.04-1.57. The Principal Investigator of CARET, Dr Gilbert Omenn, stated that former smokers, who comprised 34 percent of the participants when recruited, may have responded more favorably to vitamin A and β-carotene than current smokers. Dr Charles Hennekens stated that in the Physicians' Health Study β-carotene supplements had no significant effect – positive or negative – on cancer or cardiovascular disease, in his population of mostly nonsmokers. In response to these findings, investigators of the Women's Health Study[140] decided to remove β-carotene from their intervention, and continue with vitamin E and aspirin. Publication of the results from CARET and the Physicians' Health Study are anticipated by Spring 1996. We feel this new information strengthens the conclusions reached in this review.